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INTOXICATION UPON ACQUIRED
RESISTANCE TO PNEUMOCOCCAL
INFECTION IN RABBITS

A DISSERTATION SUBMITTED TO THE FACULTY OF THE
DIVISION OF THE BIOLOGICAL SCIENCES IN CANDI-
DACY FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF PATHOLOGY
MARCH, 1942

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The effects of alcoholic intoxication upon immunological processes have been investigated since Koch (1), in 1884, observed higher fatality-rates during cholera-epidemics among excessive users of alcohol, and concluded, therefore, that alcoholic intoxication depresses the immune mechanisms in man. Although an extensive literature on this subject has developed since then, no attempt to review it will be made in this paper, as this has been well done recently (2).

The present study of the effect of alcoholic intoxication in the rabbit upon acquired resistance to pneumococcal infection was undertaken in an effort to determine (1) in what ways alcoholic intoxication might influence the mechanisms of active immunity, and (2) to what extent large amounts of antibody might tend to counteract the loss of resistance caused by alcohol. Previous investigations have neglected this phase of the problem and hence have failed to supply important information necessary for the adequate treatment of infections in alcoholic patients.

MATERIALS AND METHODS

In the course of this study, 120 rabbits, averaging 2100 grams, were used. Of these, 56 were actively immunized, 20 were passively immunized, and 44 were non-immune. All, except 22 of the non-immune animals, were infected at the beginning of the experiment. These 22 rabbits were given the same amount of alcohol given to the infected animals, in order to determine whether that amount or the technic used in its administration would cause death. Alcohol was given in intoxicating doses to 34 actively immunized animals and to 15 passively immunized ones, in addition to the 22 non-immune animals already mentioned.

Active immunity was produced by the injection of a formalin-killed, 18-hour broth-culture of Type 1 pneumococci. This strain, known as A5, was also used to infect the animals later. It has been used extensively by O. H. Robertson (3) and is highly virulent for rabbits. The injections of 1 ml of vaccine were given five days apart, twice subcutaneously, twice intraabdominally, and once intravenously. The resulting agglutinative titers of these animals and of those passively immunized were determined macroscopically as follows: Seven progressive dilutions of freshly obtained blood serum, ranging from 1-20 to 1-1280, were mixed in 1 ml quantities with 1 ml of vaccine approximately of the density of No. 4 Barium Sulfate Standard (McFarland). After the mixed suspensions had stood for a half an hour at room-temperature, they were centrifuged for

four minutes. The tubes were then shaken to resuspend the particles. Large flakes or small particles of agglutinated pneumococci were considered positive. A granular resuspension was called a trace (tr). Actual resuspension of the vaccine with a resultant cloudy, evenly dispersed mixture indicated no agglutination. Paratyphoid vaccine was used as a control along with tubes of saline solution and pneumococcal vaccine without serum.

Passive immunity was produced by a single intravenous injection of 1 ml of immune rabbit-serum equivalent to 4500 units of antibody,¹ an amount found adequate for protection against the infecting dose of 0.1 ml of a 6-8 hour broth-culture of Type 1 pneumococci.

Alcohol was administered orally to the rabbits by stomach-tube in amounts sufficient to produce a stuporous condition bordering on coma. Usually 50-60 ml of 24 per cent alcohol were required. Intoxication was maintained by giving additional alcohol as needed. Blood-levels of 400-600 mg of alcohol/100 ml of whole blood were obtained by the method of Levine and Bodansky (4).

The infection was started two hours after intoxication was begun and four hours after passive immunization, by the intracutaneous inoculation on the flank, of 0.1 ml of a 6-8 hour broth-culture of live pneumococci.

One set of animals, comprising members from all the infected groups, was sacrificed at the end of 6 hours of infection and the skin at the site of inoculation taken for microscopic study. For this experiment, non-immune rabbits were intoxicated and infected for the study of their lesions. The skin was fixed in Zenker's fluid with 10 per cent acetic acid and stained by the Gram stain of Weigert as modified by Wallace (5).

An additional experiment was done in which the rabbits received large amounts of immune serum. In this experiment, seven rabbits, averaging about 2 kilograms, were used. One received no serum and was used as a non-immune control. Two received 4500 units of antibody; one being used as an immune control, and one as an intoxicated immune animal. The remaining four animals were given 9000, 13500, 18000, and 23500 units of antibody respectively. One hour after receiving the serum they were all bled for the titration of the sera for antibody and then intoxicated with alcohol. They were maintained in a stupor for 45 consecutive hours. One hour after the intoxication, all the animals were infected with the organism.

RESULTS

The animals were observed for the purpose of maintaining the intoxication and watching the course of the dermal lesions, and those dying were autopsied and the blood cultured. A positive blood-culture of pneumococci was taken as evidence of death from pneumococcus septicemia. The experiment was considered completed at the end of 90 hours, since no deaths occurred in any ani-

¹ Kindly donated by Lederle Laboratories, Inc.

mals beyond this time. Both active and passive immunization protected the rabbits adequately from the infection when no alcohol was given.²

In table 1, the total deaths and death-rates of the six groups of animals used in this experiment are tabulated. The significant fact to be noted is the marked difference in the death-rates of the alcoholic actively and passively immunized animals. Although the passively immunized intoxicated animals died of their infection, only half of the similarly treated actively immunized animals died. Of these, one animal had a negative blood-culture, and may have died of inter-current infection in the lungs. This marked variance in the death-rates of the two groups indicates a marked difference in the influence of alcoholic intoxication upon the degree of resistance afforded by the two methods of immunization.

TABLE 1

Total deaths and death rates of the six groups of animals used in the experiment

GROUP		NO. OF ANIMALS	NO. DIED	NO. SURVIVED	PER CENT DIED
Immunity	Intoxicated				
Active.....	Yes	34	17	17	50
Active.....	No	22	1	21	4.5
Passive.....	Yes	15	15	0	100
Passive.....	No	5	0	5	0
None.....	No	22	22	0	100
Uninfected.....	Yes	22	2*	20	9

* One animal died from passage of the tube into the lung.

TABLE 2

The average period of survival after infection of the animals that died during the experiments

GROUP	NO. OF ANIMALS	EARLIEST DEATH	LATEST DEATH	AVERAGE SURVIVAL-PERIOD
		hours	hours	hours
Intoxicated active immune rabbits...	17	29	72	45
Intoxicated passive immune rabbits...	15	30	40	36
Non-immune non-intoxicated rabbits.	22	14	29	23

This difference becomes more apparent when the average periods of survival are calculated, as in table 2. Non-immune rabbits without alcohol died, on the average, 23 hours after infection. The earliest death in this group occurred at 14 hours, the latest at 29 hours. Intoxicated passively immunized rabbits died, on the average, 36 hours after infection. The intoxicated actively immunized rabbits lived the longest, dying, on the average, 45 hours after infection, and some as late as 72 hours. The longest survival-time of any passively immunized intoxicated rabbit was but 40 hours. Obviously, the active immuni-

² The one actively immunized animal that died in the absence of alcoholic intoxication, succumbed to a septicemia after 84 hours following the injudicious location of the site of infection over a large surface vessel.

zation was more effective than the passive immunization in counteracting the effect of alcoholic intoxication upon the resistance of the animals.

The antipneumococcal antibody-content of the serum of the different animals was determined. These data are tabulated on table 3. It should be noted that, when the titer of antibody present in the serum of an actively immunized animal equaled that found in the passively immunized animals, both animals survived for about the same period of time. The survival-time of those animals which died during the course of the infection is roughly proportional to the amount of antibody present in the serum, and, since this titer in the actively immunized animals averaged approximately 1-640 dilution, while that of the

TABLE 3
Antipneumococcal antibody-content of serum as shown by agglutinative titer

RABBIT	DILUTION							REMARKS
	1-20	1-40	1-80	1-160	1-320	1-640	1-1280	
AAI	+	+	+	+	+	tr	-	Survived
AAI	+	+	+	tr	-	-	-	Survived
AAI	+	+	tr	-	-	-	-	Died at 34 hr
AAI	+	+	±	-	-	-	-	Died at 36 hr
AAI	+	+	+	+	+	+	+	Survived
AAI	+	+	+	+	+	tr	-	Died at 62 hr
AAI	+	+	+	+	+	+	-	Survived
AAI	+	+	+	+	+	tr	-	Died at 60 hr
NAAI	+	+	+	tr	-	-	-	Survived
NAAI	+	+	+	tr	-	-	-	Survived
NANI	-	-	-	-	-	-	-	Died at 18 hr
NANI	-	-	-	-	-	-	-	Died at 17 hr
API	+	+	tr	-	-	-	-	Died at 36 hr
API	+	+	tr	-	-	-	-	Died at 32 hr
API	+	+	tr	-	-	-	-	Died at 40 hr
API	+	+	-	-	-	-	-	Died at 30 hr
NAPI	+	+	tr	-	-	-	-	Survived
NAPI	+	+	+	-	-	-	-	Survived

AAI, alcoholic actively immunized rabbit; NAAL, non-alcoholic actively immunized rabbit; API, alcoholic passively immunized rabbit; NAPI, non-alcoholic passively immunized rabbits; NANI, non-alcoholic non-immune rabbit.

passively immunized animals reached only 1-80 dilution, the reason for the difference in the death-rates and survival-times of the two groups is obvious. The greater amount of antibody present in the blood of the actively immunized animals as compared to the relatively small amount present in the passively immunized animals, enabled the former group to resist the effect of alcohol more strongly than the latter.

The additional experiment described under "Materials and Methods" was done in order to check the hypothesis that the survival-time of the infected immune intoxicated animals was roughly proportional to the amount of antibody present in the serum. The data of this experiment are tabulated in

table 4. It is to be noted that as the amount of circulating antibody was increased, death from pneumococcal infection in the presence of alcoholic intoxication was delayed. When five times the amount of antibody necessary to protect the non-intoxicated animals was used, this intoxicated rabbit (#7), survived. While the number of animals in this experiment is admittedly small, the results corroborate the assumption that by increasing the amount of circulating antibody the depressing effect of alcohol upon the resistance of an animal can be delayed or actually eliminated.

Observation of the site of infection throughout the course of the experiment revealed a striking difference between the lesions of the intoxicated and non-intoxicated animals. No macroscopic lesions developed early in the intoxicated animals in contrast to the edematous and hemorrhagic lesions of the non-immune, non-alcoholized animals and to the small circumscribed hyperemic wheals of the immunized, non-alcoholized animals. The only intoxicated immune animals to develop macroscopic lesions were those that survived the infection and intoxication. The lesions in these animals were ill-defined, slightly

TABLE 4

The effect of increased amounts of antibody on the survival-time of intoxicated rabbits infected with pneumococcus type

RABBIT NUMBER	UNITS OF ANTIBODY	ALCOHOL ?	AGGLUTININATIVE TITER	SURVIVAL-TIME
1	0	No	0	23 hours
2	4500	No	1-40	lived
3	4500	Yes	1-40	28 hours
4	9000	Yes	1-80 (tr)	36 hours
5	13500	Yes	1-160	58 hours
6	18000	Yes	1-320 (tr)	66 hours
7	23500	Yes	1-320	lived

raised, and only slightly hyperemic. They were first seen about the end of the third day. At the end of the fourth day they resembled the non-intoxicated immunized lesions that were rapidly healing at the end of the first day. The non-appearance of a macroscopic circumscribed lesion in animals that subsequently died of septicemia, indicates the inability of the intoxicated animal to localize the infection, due to the absence of the vascular inflammatory response. The final, although late, appearance of macroscopic lesions in the intoxicated actively immunized animals that survived indicates the development of a localizing mechanism probably as a result of the large amounts of antibody present in these animals.

Similarly to the macroscopic observations, the microscopic study of the six-hour lesions reveals marked differences between those of the intoxicated animals and the non-intoxicated animals, and between the intoxicated passively and actively immunized lesions. For example, there was:

1. In the *non-immune animals*, a dense leukocytic exudate showing recent hemorrhage, edema, fibrin deposition, and many pneumococci with but little or no phagocytosis (Plate I);

2. In the *passively and actively immunized animals*, a very dense leukocytic exudate with active phagocytosis of the organisms, no hemorrhage or discernible edema, rare extra-cellular organisms in the actively immunized, and occasional extracellular organisms in the passively immunized lesions (Plates II and III);

3. In the *intoxicated non-immune animals*, a very few leukocytes, edema but little hemorrhage, and organisms growing abundantly and diffusely throughout the sections (Plate IV);

4. In the *intoxicated passively immunized animals*, fewer leukocytes than in the non-intoxicated passively immunized animals or the intoxicated actively immunized animals, with active phagocytosis but many persisting extracellular organisms, many of which were growing in clumps (Plate V); and

5. In the *intoxicated actively immunized animals*, fewer leukocytes than in the non-intoxicated animals, which were slightly more abundant than in the intoxicated passively immunized animals, and active phagocytosis and agglutination of the extracellular organisms, which were more abundant than in the non-intoxicated actively immunized animals but were less prominent than in the passively immunized, intoxicated animals (Plate VI).

The difference between the lesions of the intoxicated and non-intoxicated animals consists mainly in the reduced numbers of leukocytes and the increased numbers of extra-cellular organisms present in the former. It is significant, also, that, in the lesions of the three groups of intoxicated animals; namely, the non-immunized, passively immunized, and actively immunized animals, there is a parallelism between the relative antibody-titers of these three groups and their resistance to the infection in the presence of alcohol. Of these groups, the reduction in number of leukocytes and the increase in number of extracellular organisms is greatest in the first, less marked in the second, and least marked in the third group, while the resistance to the infection and the relative antibody-titers are lowest in the first, low in the second, and high in the third group.

DISCUSSION

The pneumococcal dermal lesion in the rabbit affords an excellent opportunity to study the cellular immune processes because of (1) the high infectivity of this disease in the normal rabbit; (2) the rapid fulminating course with a terminal septicemia, and (3) the adequate protection against it that either passive or active immunization is able to produce.

When intoxicated with alcohol, passively immunized rabbits lose this protection, as Pickrell (2) showed in experiments in which all non-intoxicated passively immunized rabbits survived the infection with pneumococci while all similarly treated intoxicated rabbits died. His experiments, however, utilized relatively small amounts of antibody and were not designed to investigate the aspects of alcoholic intoxication and resistance in general. Active immunization by engendering the continuous production of large amounts of antibody, should make an animal less susceptible to alcoholic action than passive immunization.

Alcoholic intoxication has been shown to depress native or natural resistance of rabbits to cholera (Koch 6, Doyen 7, Thomas 8, Delearde 9), to streptococci and pneumococci (Rubin 10), and to diphtheria and pus-forming cocci (Valagussa and Raneletti 11). Its effect upon acquired resistance necessitates any hypothesis concerning the mode of action in this destruction to explain the loss of resistance in immune as well as in non-immune animals. From the practical point of view, such an explanation would be of service in the successful treatment of infection in alcoholic patients.

Alcoholic intoxication may reduce resistance to infection, even in the presence of antibodies, either by (1) destruction of the antibody by the alcohol, and/or (2) interference with the cellular mechanisms of defense.

The possibility of alcohol destroying antibodies can be ruled out, since it has been shown that alcoholic intoxication does not destroy antibodies already produced (Delearde 9). Even in a concentration of 6 per cent alcohol, agglutination of bacteria by antibody occurs *in vitro* (Franzen 12). In the present study the lesions of the intoxicated immune animals showed both an accelerated phagocytosis and effective agglutination of bacteria, ample proof of the presence and activity of antibody undestroyed by alcohol.

On the other hand, interference with the cellular mechanisms of defense does occur during alcoholic intoxication, and is probably the method by which alcohol exerts its effect. Pickrell (2) suggested that alcohol paralyzes the vascular inflammatory response: as a result the leukocytes fail to enter the area of infection, thus allowing the bacteria to multiply uninterruptedly. Cressman and Rigdon (13) reached a similar conclusion in their study of the effect of alcoholic intoxication on the inflammatory response to xylol and aleuronat, but differed with Pickrell in the degree of this paralysis, which is not complete, since some leukocytes do reach the area of inflammation. In the present study, leukocytes reached the area of inflammation in reduced numbers in the presence of alcoholic intoxication, but these numbers were significant in the presence of active immunity. The absence of edema and hyperemia at the site of infection implies some such action as decrease in vascular permeability and interference with the vascular inflammatory response, but actual proof is lacking on this point. A study, now in process and to be reported later, of the effect of alcoholic intoxication upon the vascular inflammatory response to infection in the *in vivo* "capillary chamber" in the ears of rabbits, contains evidence of change in permeability of the capillaries and obstruction to the emigration of leukocytes in the presence of alcoholic intoxication.

The presence of phagocytosis in the lesions of the intoxicated immune animals is evidence that this immune mechanism is not destroyed by alcohol. This has been a disputed point. Many investigators concluded that alcohol decreased phagocytosis, while others observed no effect. The former, however, used amounts of alcohol in *in vitro* studies which are never reached in the body during intoxication. Thus, Parkinson (14) and Kruschilin (15) demonstrated that alcohol has no effect on phagocytosis unless present in such quantities as to in-

jure seriously the vitality of the leukocyte and it is impossible for the content of alcohol in the blood of the living animals to reach this level.

Since alcoholic intoxication does not harm antibodies or the mechanisms dependent on them, but limits the number of leukocytes reaching the area of inflammation, it is evident that the loss of resistance during alcoholic intoxication is related to interference with the local inflammatory response. The presence of antibodies is antagonistic to the effect of alcohol on resistance. Uninjured by the alcohol, the antibodies accelerate the sluggish inflammatory response, enabling significant numbers of leukocytes to reach the area of inflammation, where phagocytosis is enhanced by the opsonin-effect and by the agglutination of the organisms to one another and to the tissues. When not enough antibody is present, the infection is not held in check long enough for a sufficient number of leukocytes to reach the infected site and dispose of the organisms. This failure was seen in the deaths of all of the intoxicated rabbits immunized with 4500 units of antibody. When more antibody is present, either death is delayed, or, as in the case of the immunized animals with high titers, the infection is held in check until enough leukocytes reach the infected site, dispose of the organisms, and thus enable the animal to survive. This effect was seen in the delayed deaths and survival of some of the highly immune animals.

Clinically, the death-rate of alcoholic patients with pneumonia is considerably higher than that of abstainers, and the treatment is proportionately difficult. The present study indicates that the amount of antibody that is capable of protecting the normal animal during an infection is not sufficient to protect the alcoholic animal, and thus it may explain the poor response of alcoholic patients to immune serum therapy and serve as an experimental confirmation that alcoholism is an indication for "double dose" treatment. Administration of anti-serum probably should be repeated more frequently in the infected alcoholic patient than is necessary in the treatment of the abstainer.

CONCLUSIONS

1. Alcoholic intoxication lowers resistance to infection, in that rabbits, whether actively or passively immunized against Type 1 pneumococci, died with a septicemia after dermal infection with pneumococci of the same strain.
2. Alcoholic intoxication reduces resistance by inhibiting the rapid mobilization of the local inflammatory response: consequently the micro-organisms multiply too rapidly for the reduced number of leukocytes entering the infected site to destroy them, even in the presence of active immunity, except where this immunity is unusually high.
3. The lowered resistance of infected rabbits intoxicated with alcohol can be bolstered with large amounts of specific antibody. This is seen in the survival of the actively immunized animals with high titers and the one passively immunized animal that received five times the necessary amount of antibody needed to protect a normal animal. This greater amount of antibody probably holds the infection localized long enough for the sluggish tissue defenses to

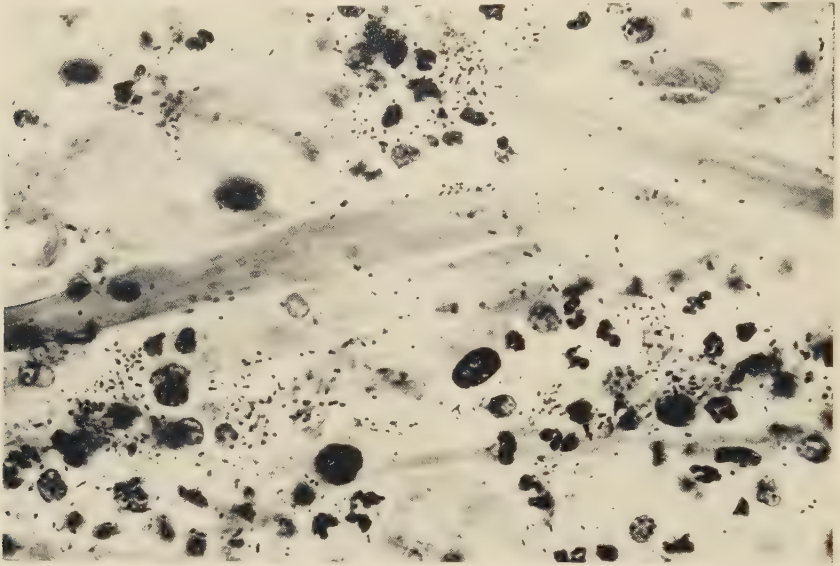
mobilize and thus is the deciding factor in the intoxicated immune animals' resistance to infection.

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PLATE I

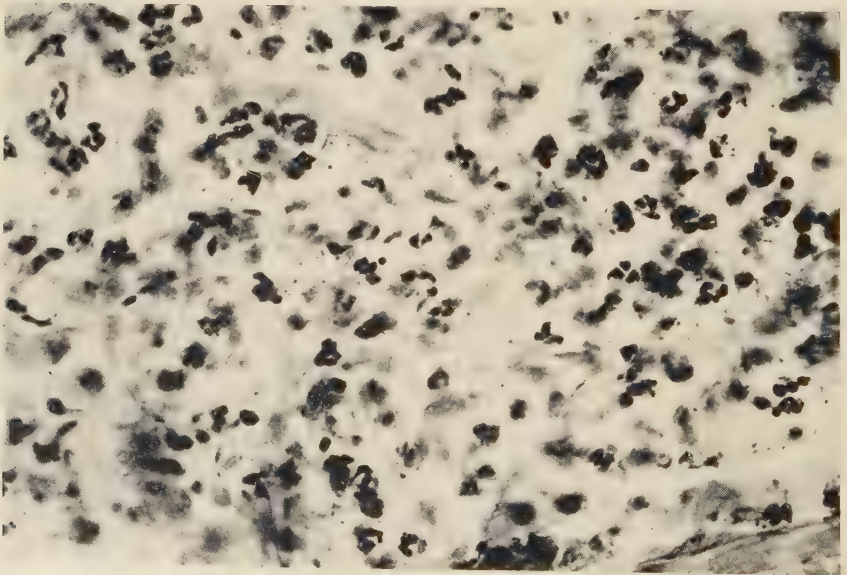
PHOTOMICROGRAPH OF A TYPICAL AREA IN THE PNEUMOCOCCAL DERMAL LESION
OF A NON-IMMUNE, NON-INTOXICATED RABBIT SIX HOURS AFTER INFECTION



This area shows many leukocytes, occasional red cells and fibrin, and many extra-cellular pneumococci. There is no phagocytosis present (magnification $\times 1000$).

PLATE II

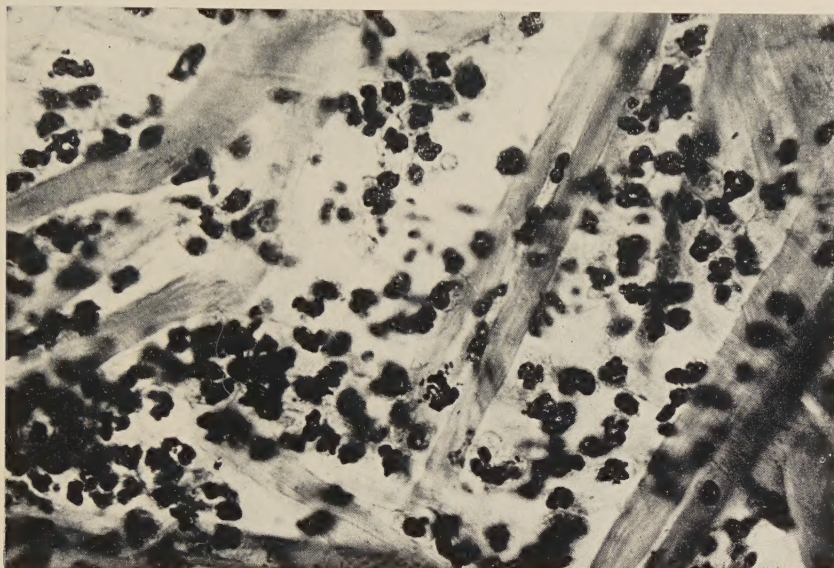
PHOTOMICROGRAPH OF A TYPICAL AREA IN THE PNEUMOCOCCAL DERMAL LESION
OF A PASSIVELY IMMUNIZED, NON-INTOXICATED RABBIT SIX HOURS AFTER
INFECTION



The area is filled with leukocytes, many of which contain pneumococci. There are relatively few extra-cellular organisms (magnification $\times 1000$).

PLATE III

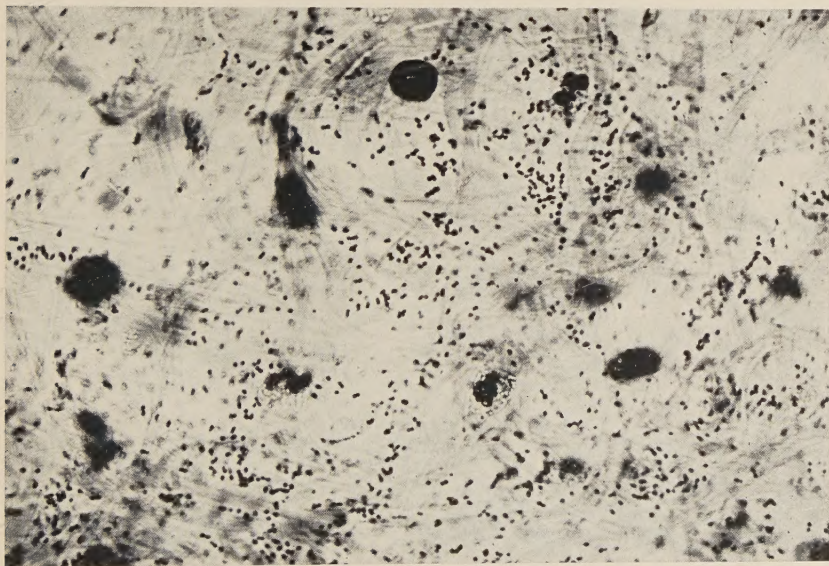
PHOTOMICROGRAPH OF A TYPICAL AREA IN THE PNEUMOCOCCAL DERMAL LESION
OF AN ACTIVELY IMMUNIZED, NON-INTOXICATED RABBIT SIX HOURS AFTER
INFECTION



The leukocyte exudate is very dense. Marked phagocytosis is present. Extra-cellular pneumococci are rare (magnification $\times 1000$).

PLATE IV

PHOTOMICROGRAPH OF A TYPICAL AREA IN THE PNEUMOCOCCAL DERMAL LESION
OF AN ALCOHOLIC INTOXICATED, NON-IMMUNE RABBIT, SIX HOURS AFTER
INFECTION



The lesion contains very few leukocytes. No phagocytosis is present. Pneumococci are spreading and proliferating rapidly (magnification $\times 1000$).

PLATE V

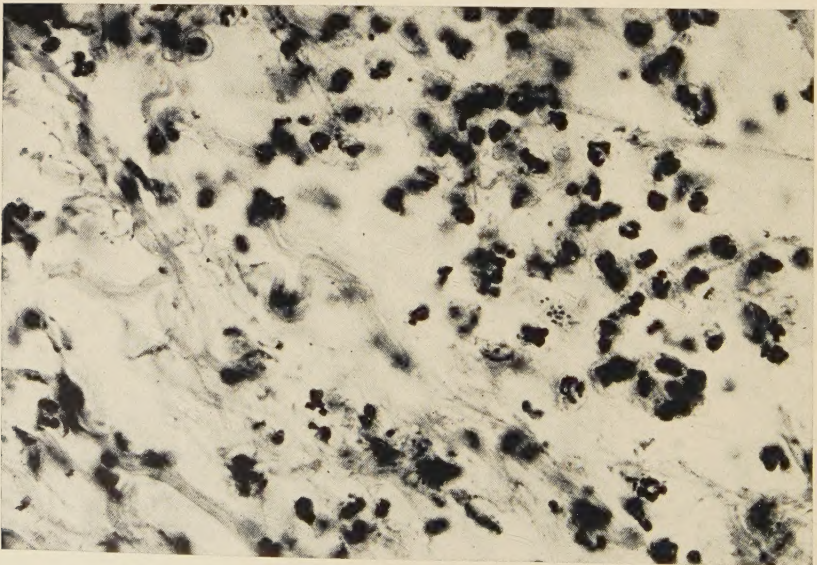
PHOTOMICROGRAPH OF A TYPICAL AREA IN THE PNEUMOCOCCAL DERMAL LESION
OF AN ALCOHOLIC INTOXICATED, PASSIVELY IMMUNIZED RABBIT, SIX HOURS
AFTER INFECTION



Fewer leukocytes and more extra-cellular pneumococci are present here than in the non-intoxicated passively immunized lesion, and the intoxicated actively immunized lesion. Phagocytosis is present (magnification $\times 1000$).

PLATE VI

PHOTOMICROGRAPH OF A TYPICAL AREA IN THE PNEUMOCOCCAL DERMAL LESION
OF AN ALCOHOLIC INTOXICATED, ACTIVELY IMMUNIZED RABBIT, SIX HOURS
AFTER INFECTION



While fewer leukocytes are present here than in the non-intoxicated actively immunized lesion, they are more numerous than in the intoxicated passively immunized lesion. Phagocytosis is present. Few extra-cellular pneumococci remain. One agglutinated clump of pneumococci is seen near the center of the field (magnification $\times 1000$).

